Complete Summary

GUIDELINE TITLE

Practice parameter: treatment of nervous system Lyme disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology.

BIBLIOGRAPHIC SOURCE(S)

Halperin JJ, Shapiro ED, Logigian E, Belman AL, Dotevall L, Wormser GP, Krupp L, Gronseth G, Bever CT Jr. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2007 Jul 3;69:1-12. [66 references]

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- September 11, 2007, Rocephin (ceftriaxone sodium): Roche informed healthcare professionals about revisions made to the prescribing information for Rocephin to clarify the potential risk associated with concomitant use of Rocephin with calcium or calcium-containing solutions or products.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Nervous system Lyme disease, including
  - Meningitis, cranial neuritis, and radiculoneuritis
  - Parenchymal inflammation of the brain or spinal cord
  - Mild radiculoneuropathy presenting as diffuse, predominantly sensory peripheral neuropathy
  - Encephalopathy
- Post-Lyme syndrome

GUIDELINE CATEGORY

Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Neurology
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide evidence-based recommendations on the treatment of nervous system Lyme disease and post-Lyme syndrome

TARGET POPULATION

Adults and children with nervous system Lyme disease or post-Lyme syndrome

INTERVENTIONS AND PRACTICES CONSIDERED

1. Antibiotics for treatment of nervous system Lyme disease
   - Parenteral (penicillin, ceftriaxone, cefotaxime)
   - Oral (doxycycline, amoxicillin, cefuroxime axetil)
2. Prolonged courses of antibiotics for treatment of post-Lyme syndrome (considered, but not recommended)

MAJOR OUTCOMES CONSIDERED

- Efficacy and duration of therapy
- Adverse effects of therapy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

In May 2004, a literature search was performed (all languages) using Ovid MEDLINE, Pubmed, and EMBASE, using search terms "Lyme Disease/[Drug Therapy, Therapy]," "Borrelia Infections/[Drug Therapy, Therapy]," "Borrelia burgdorferi group/ and (borreliosis or Borrelia or neuroborreliosis)," and "Anti-Infective Agents/[Therapeutic Use] and (antibiotic$ or antimicrob$ or anti-microb$)." This resulted in 353 citations. After elimination of duplicate citations, each abstract was reviewed by at least two members of the panel for relevance for further review. Any disagreements were arbitrated by a third reviewer. This resulted in a list of 112 articles, each of which was then reviewed by at least two members of the panel. Members of the panel recommended adding 10 additional references. After detailed review of all 122, the panel decided 37 articles contributed relevant, assessable data. Articles were excluded if they did not address treatment of neuroborreliosis, were not peer reviewed, or were solely review articles. The selected articles were then reviewed in detail by all panel members to assess the quality of the evidence contained.

NUMBER OF SOURCE DOCUMENTS

37 articles contributed relevant, assessable data.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Classification of Evidence for Therapeutic Intervention

Class I: Prospective, randomized, controlled clinical trial (RCT) with masked outcome assessment, in a representative population. The following are required:

a. Primary outcome(s) clearly defined
b. Exclusion/inclusion criteria clearly defined
c. Adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias
d. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR an RCT in a representative population that lacks one criterion a–d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.*

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Studies were divided into three groups: adult Lyme disease, pediatric Lyme disease, and post-Lyme syndrome. Each article was reviewed to determine if it specifically addressed treatment of neuroborreliosis, and if it contained original data. Those that were relevant were then graded as Class I through IV, using standard criteria, as listed in the "Rating Scheme for the Strength of the Evidence" field. An evidence table was constructed listing each study, its class, the treatment regimens assessed, whether it was prospective or retrospective, whether it was blinded or open, whether it was controlled or not, whether it used explicit or objective response criteria, the number of subjects, the duration of observation, the completeness of follow-up, and the outcomes.

Overall, four studies were Class I (three in post-Lyme syndrome). One, performed in children, was considered Class I with regard to its predetermined outcome measure, cerebral spinal fluid (CSF) antibiotic levels, but this study did not discuss clinical outcomes. Four studies were Class II (three in adults with neuroborreliosis, one in children). All were rated Class II with regard to at least one of their predetermined objective measures of disease activity: enzyme-linked immunosorbent assay (ELISA), CSF cell count or culture, all of which were apparently measured in masked fashion. All four of these studies would be considered Class III with regard to clinical outcomes, for which assessments were not masked. All other studies were Class III or IV.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In the spring of 2004 the Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN) convened an expert panel of investigators from the United States and Europe who have published extensively in the field. The panel was selected to represent a broad range of relevant expertise and opinion.

The relevant literature was reviewed in detail to determine the following:

1. Which antimicrobial agents have been shown to be effective or ineffective in the treatment of nervous system Lyme disease
2. If different regimens are preferred for different manifestations of neuroborreliosis
3. What duration of therapy is needed

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Classification of Recommendations

A = Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment is unproven.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guideline was approved by the Quality Standards Subcommittee on July 29, 2006; by the Practice Committee on March 15, 2007; and by the American Academy of Neurology Board of Directors on April 5, 2007.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the strength of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

Conclusions

Neuroborreliosis (Adult and Pediatric)

Based on four Class II studies antibiotic regimens have been established as probably safe and effective for both children and adults. One Class I and one Class II study suggest that parenteral regimens are probably safe and effective for severe neurologic disease but two Class II studies and numerous Class III and IV studies suggest that oral treatment, particularly with doxycycline, is comparably safe and effective in many situations not involving parenchymal central nervous system (CNS) involvement. Although the evidence is stronger in adults than children, all available evidence indicates that the responses to oral treatment are comparable in adults and children. However, it must be emphasized that no definitive data exist to establish the superiority—or lack thereof—of either oral or parenteral treatment. Specific regimens are listed in tables 1 and 2 in the original guideline document.

Post-Lyme Syndrome

Several Class I studies indicate that the disorder referred to as post-Lyme syndrome does not respond to prolonged courses of antibiotics and that such treatment can be associated with serious adverse events (see "Potential Harms" field).

Recommendations

1. Parenteral penicillin, ceftriaxone, and cefotaxime are probably safe and effective treatments for peripheral nervous system Lyme disease and for CNS Lyme disease with or without parenchymal involvement (**Level B recommendation**).
2. Oral doxycycline is probably a safe and effective treatment for peripheral nervous system Lyme disease and for CNS Lyme disease without parenchymal involvement (**Level B recommendation**). Amoxicillin and cefuroxime axetil may provide alternatives but supporting data are lacking.
3. Prolonged courses of antibiotics do not improve the outcome of post-Lyme syndrome, are potentially associated with adverse events, and are therefore not recommended (**Level A recommendation**).

Definitions:

Classification of Recommendations

A = Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment is unproven.

Classification of Evidence for Therapeutic Intervention

Class I: Prospective, randomized, controlled clinical trial (RCT) with masked outcome assessment, in a representative population. The following are required:

a. Primary outcome(s) clearly defined
b. Exclusion/inclusion criteria clearly defined
c. Adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias
d. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR an RCT in a representative population that lacks one criterion a–d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.*

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of antibiotics to treat nervous system Lyme disease and post-Lyme syndrome

POTENTIAL HARMS

Comment on Treatment Safety

- Although the antimicrobial regimens discussed are widely used and generally well tolerated, none is without potential side effects. In one of the studies of post- Lyme syndrome, 12 of the 28 patients receiving ceftriaxone developed diarrhea, while 4 developed allergic reactions (1 anaphylaxis, 3 minor). Because of its biliary excretion, ceftriaxone tends to cause pseudolithiasis (precipitation of the drug in the gall bladder), and may be associated with pseudomembranous colitis more frequently than other antimicrobials. Of the 55 patients (treated and placebo) who had indwelling intravenous (IV) access catheters, 3 developed line sepsis (1 of 28 on ceftriaxone). One other treated patient in this study developed anaphylaxis while 10 developed less severe adverse events. In the other published pair of long-term treatment trials, 27 of 129 patients developed adverse effects (16 of 64 receiving ceftriaxone), 2 of which (both patients on ceftriaxone) were life threatening (1 pulmonary embolism, 1 fever and gastrointestinal [GI] bleed). Combining treated patients in these three studies, life-threatening complications occurred in 1 per 23, while overall, adverse events occurred in about 1 of every 3 treated patients.
- Although oral doxycycline avoids issues related to line infections, the drug is associated with gastric irritation and with photosensitization. The latter is particularly problematic since most acute manifestations of Lyme disease occur in summer and autumn. Tetracyclines also cause abnormalities of developing bones and teeth in the fetus and in children under age 8.

CONTRAINDICATIONS

CONTRAINDICATIONS

Tetracyclines (including doxycycline) are relatively contraindicated in children <8 years of age or in pregnant or lactating women.

QUALIFYING STATEMENTS

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This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative

methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Halperin JJ, Shapiro ED, Logigian E, Belman AL, Dotevall L, Wormser GP, Krupp L, Gronseth G, Bever CT Jr. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2007 Jul 3;69:1-12. [66 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Jul

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Quality Standards Subcommittee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: J.J. Halperin, MD; E.D. Shapiro, MD; E. Logigian, MD; A.L. Belman, MD; L. Dotevall, MD; G.P. Wormser, MD; L. Krupp, MD; G. Gronseth, MD; C.T. Bever Jr., MD

Quality Standards Subcommittee Members: Jacqueline French, MD, FAAN (*Co-Chair*); Gary S. Gronseth, MD (*Co-Chair*); Charles E. Argoff, MD; Stephen Ashwal, MD, FAAN (ex-officio); Christopher Bever, Jr., MD, MBA, FAAN; John D. England, MD, FAAN; Gary M. Franklin, MD, MPH (ex-officio); Gary H. Friday, MD, MPH, FAAN; Larry B. Goldstein, MD, FAAN; Deborah Hirtz, MD(ex-officio); Robert G. Holloway, MD, MPH, FAAN; Donald J. Iverson, MD, FAAN; Leslie A. Morrison, MD; Clifford J. Schostal, MD; David J. Thurman, MD, MPH; William J. Weiner, MD, FAAN; Samuel Wiebe, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least three AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

The authors report no conflicts of interest.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the American Academy of Neurology Web site.
- Practice parameter: treatment of nervous system Lyme disease. AAN summary of evidence-based guidelines for clinicians. St. Paul (MN): American Academy of Neurology. 2007. 2 p. Available in Portable Document Format (PDF) from the AAN Web site.

PATIENT RESOURCES

The following is available:

- Treatment of nervous system Lyme disease. AAN guideline summary for patients and their families. St. Paul (MN): American Academy of Neurology (AAN). 1 p.

Electronic copies: Available in Portable Document Format (PDF) from the AAN Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI Institute on July 6, 2007. This summary was updated by ECRI Institute on October 3, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Rocephin (ceftriaxone sodium).

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